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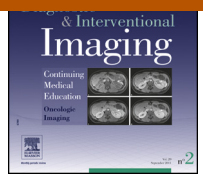

CONTINUING EDUCATION PROGRAM: FOCUS...

MR perfusion for pelvic female imaging

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Abstract Perfusion MRI of the female pelvis is based on a T1-weighted imaging acquired repeatedly at high temporal resolution. Post-processing can be carried out either from a visual analysis, by description of the curves or by compartmental modeling. Many studies have shown this method to be useful in detecting cervical cancers (initial tumor or identification of recurrence), and in staging endometrial cancers (assessment of cervical invasion). More recent studies have described perfusion MRI as a tool for characterizing adnexal tumors based on the properties of the microvascular wall. When it is combined with morphological MRI findings and diffusion sequences, it incorporates a decision-making algorithm which has a diagnostic performance of 95.4% in characterizing complex adnexal masses (Thomassin-Naggara et al., 2011).

''Contrast enhanced'' Magnetic Resonance Imaging (MRI) has advanced because of perfusion, blood volume and capillary permeability which depend on the quality of the vascular walls. MRI therefore offers an in vivo functional examination, providing information on the structure and function of the tumor microvasculature. Many MRI techniques are used to study angiogenesis: with endogenous contrast (the BOLD effect, or spin labeling) or using an exogenous contrast medium (gadolinium chelates, which diffuse into the extracellular space and more recently, long lasting vascular gadolinium macromolecules, SPIO and USPIO). In pelvic imaging, dynamic contrast studies are performed mostly in a T1-weighted sequence because of the poorer spatial resolution of techniques such as spin labeling or the BOLD effect.

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The educational aims of this review are to describe the sequences and post-processing which can be used in contrast enhanced dynamic imaging in the female pelvis, to consider the used of dynamic contrast enhanced MRI in uterine diseases and to characterize adnexal tumors and to incorporate these findings into usual practice to determine the added value of this MRI mode in clinical diagnostics.

Types of dynamic contrast enhanced MRI sequences after data processing

Sequences

General details

''The best sequence would be one which achieves the best compromise between good spatial resolution and good temporal resolution''. Most studies in pelvic imaging define diagnostic criteria based on changes in contrast enhancement in the first two minutes after injection, with a temporal resolution of under 15 s. Because of this time constraint, it is not always possible to investigate a large volume, as may be necessary in adnexal disease, to give an example. In addition, dynamic contrast enhanced MRI must offer good spatial resolution in order to enable a detailed analysis of the extension of endometrial cancer or assessment of contrast enhancement of small growths in adnexal tumors.

When machine performances permit, the optimal sequence is therefore an isotropic 3D gradient echo sequence in order to enable multiplanar reconstructions to be made, covering a sufficient volume to be independent of the initial analysis of morphological sequences. In practice, if this type of sequence does not provide a temporal resolution of under 15 s, the alternative is to use a 2D gradient echo sequence and an acquisition plane containing the structure to be examined and the internal reference point (for example, the adjacent myometrium in the investigation of adnexal tumors) on gadolinium-enhanced morphological sequences.

Dynamic gadolinium contrast studies should be as reproducible as possible and are therefore ideally performed with an automated injector using a dose of 0.01 mmol/kg of contrast rinsed with 20 cc of physiological saline.

Specific features depending on the organ being examined

In our clinical practice, we use a 2D T1-weighted echo gradient sequence (FLASH 2D) with the following parameters (RT/ET: 27/2.24 ms; flip angle: 80°; section thickness: 5 mm; number of sections: 3; excitations: 1; FOV: 400—200 mm and matrix: 256 × 134; BW: 300).

Upper and lower saturation bands are positioned on either side of the acquisition box to limit inflow effect and venous flow artifacts.

In order to study the uterus, the dynamic contrast enhanced MRI sequences should preferably be positioned and acquired in the sagittal plane in order to visualize the whole endometrial-myometrial interface.

To study the adenexae, we position the section box in order to acquire both the solid component of the adnexal tumor and the adjacent external myometrium. The box may therefore range in position from being strictly axial to coronal, including all types of oblique axial planes.

Processed data analysis and limitations of acquisitions

Analysis of enhancement kinetics

Several enhancement kinetic analyses are possible for T1-weighted gadolinium dynamic contrast enhanced MRI (DCE-MRI):

- the simplest method involves describing the shapes of the enhancement curves, which may or may not be compared to the enhancement curve of the reference organ [1]. For pelvic imaging, some authors have proposed using the striated pelvic wall muscles as the internal reference. In our opinion, this tissue is a poor reference point. In order for a tissue to be a good reference, it should lie within the study field, have consistent perfusion in different people (variations in muscle perfusion in correlation with muscular atrophy can be observed) and the enhancement of the reference tissue should be similar to that of the tissue being examined (this does not apply to striated muscle which has very low enhancement). In our experience, the external myometrium fulfills two of these three conditions satisfactorily. It is located close to the pelvic organs and has a similar enhancement curve to that of the endometrium or the solid part of ovarian tumors. On the other hand, there are significant differences in all of the perfusion parameters depending on hormone status, all of them declining at the menopause [2]. This must be taken into account when enhancement curves are examined;
- the second form of processed data analysis involves adjusting the enhancement curve using a mathematical equation which contains parameters describing the curve, such as the asymptote, the ascension half time, the maximum gradient and the area under the curve. The area under the enhancement curve is considered to be the most robust parameter and is often used in longitudinal studies examining the efficacy of medicinal products on tumors. These are more reproducible parameters than a simple description of the enhancement curve but are still based on signal values which are always dependent on the conditions of the acquisition (differences in radiofrequency wave, gain, settings for the sequence used [TR, TE, tilt angle]). The reference analytical method for perfusion MRI is therefore quantification of the concentration of contrast medium in the tissue compartments and exchanges of contrast medium between compartments (or compartmental modeling). This is the reference method for analysis of dynamic contrast enhanced MRI as it allows reproducible parameters to be calculated on different machines. It also enables a pathophysiological interpretation of tumor enhancement to be made, with a reliable analysis of perfusion effects. To achieve this quantification, the acquisitions must be clarified and post-processing of the data obtained must be carried out.

Data acquisition

An MRI sequence has been developed for pelvic imaging which combines the high spatial resolution (needed to

identify small tissue structures such as growths in adnexal disease) with high temporal resolution (in the region of 3 s) (the turbo-FLASH sequence). This allows each patient's specific arterial input function to be used (the criteria for post-processing quality). In addition, the tilt angle has been optimized: using high tilt angles (80°) reduces the blood signal saturation and optimizes the enhancement dynamics and linearity of the relationship between signal and gadolinium concentration.

Post-processing

Semi-automatic filtering methods for dynamic contrast enhanced MRI findings are useful for improving the acquisition signal to noise ratio both qualitatively (by visual examination) and quantitatively (post-processing of data). This method is particularly useful to map parameters and provides a less biased analysis than mapping the regions of interest.

In addition, a comparison of different pharmacokinetic models has shown that four parameter compartmental modelings (the most detailed compartmental model allowing tissue perfusion (TP), the blood volume fraction (Vb), capillary surface permeability (SP) and interstitial volume (eV)) to be calculated. This provides the most reliable description of physiological effects and optimally uses the information contained in data acquired via pelvic imaging. Software is beginning to emerge to extend the use of this type of analysis, particularly to study breast tissue perfusion (extended Tofts-Kéty modeling) and prostate (Brix model). However, this type of analysis is still experimental in pelvic gynecology.

Uterus

Healthy myometrium

The first description of healthy myometrial enhancement on dynamic contrast enhanced MRI was reported by Yamashita et al. in 1993 [3]. This landmark study described three types of myometrial behavior depending on hormone status and time of the cycle. Type 1 enhancement involved early uptake in the sub-endometrial ''halo'', the fine line of enhancement located between the endometrium and the myometrium. This was seen more often in patients during the proliferative phase of the cycle and in post-menopausal patients. Type 2 enhancement involved early uptake in the junctional zone (a thick enhancement line) which represents the internal myometrial band appearing as a hypointensity on T2-weighted sequences. Thirdly, type 3 enhancement was early uptake in whole myometrium, particularly the external portion. These latter two types of enhancement were seen more often in the luteal and menstrual phases of the cycle. A key point of this study was that it was the first to describe the types of enhancement seen in the healthy myometrium although it was only carried out in a population of 13 patients. In a study carried out by our group on 85 patients including 23 who were post-menopausal and 62 who were pre-menopausal (31 in the proliferative phase and 31 in the luteal phase), we found behavioral differences in healthy myometrium on dynamic contrast enhanced MRI. The post-menopausal patients had identical internal and external myometrial enhancement which was significantly less intense than in the pre-menopausal patients. Internal myometrial enhancement occurred earlier and was more intense in the proliferative than in the luteal phase of the cycle. Doppler ultrasound differences in internal myometrial infusion during the menstrual cycle are well described [4] and are believed to be involved in migration of spermatozoa (contraction) and in implantation. The consistent findings obtained with Doppler ultrasound and dynamic contrast enhanced MRI has opened many areas for applications in disease and fertility.

Uterine tumors

Endometrium

Yamashita's landmark article was intended to provide the first description of the use of dynamic contrast enhanced MRI to assess endometrial cancers. Tumor gadolinium enhancement was less than that of the myometrium in the early phase in most cases (80%) and tended to increase in the later sequences but remained hypointense in 70% of patients, isointense in 20% and occasionally hyperintense compared to the myometrium (in 10% of cases) [5]. Myometrial extension can be easily assessed on T2-weighted sequences in pre-menopausal patients in whom the junctional zone is traditionally clearly seen. This zone, however, changes in response to hormones. T2-weighted sequences to assess myometrial extension have a diagnostic accuracy of 80% in pre-menopausal patients compared to only 33% in post-menopausal women. This landmark study was conducted using the old FIGO classification which made three distinctions within stage 1: the former stages IA, which was strictly within the endometrium from stages IB with myometrial invasion of under 50% and stages IC with myometrial invasion of over 50%. The FIGO classification has now changed [6] and stages IA and IB are now merged. The radiologist now only has one question about stage I to answer: is myometrial invasion over or below 50%? The importance of finding an interruption in the periendometrial halo, previously described as the key sign of myometrial invasion and obtained on perfusion sequences, is no longer important. One study compared the value of T2-weighted, diffusion and perfusion MRI to assess myometrial invasion in endometrial cancer [7] and showed that merged T2-weighted and diffusion sequences were significantly superior for tumors with under 50% myometrial invasion compared to perfusion sequences alone. This improvement in performance has been confirmed in a more recent study in terms of analytical reproducibility, with a Kappa coefficient of 0.25 for perfusion MRI compared to 0.75 for diffusion [8] (Fig. 1). Gadolinium dynamic contrast enhanced MRI is still useful if cervical extension is suspected because of the poor physiological vascularization of the cervical stroma. In addition, some authors have demonstrated that dynamic contrast enhanced MRI is useful in distinguishing benign disease from endometrial cancer. The technique is useful when diagnostic hysteroscopy and biopsy cannot be performed or is non-contributory (cervical stenosis, bulky submucosal fibroids, adenomyosis, etc.).

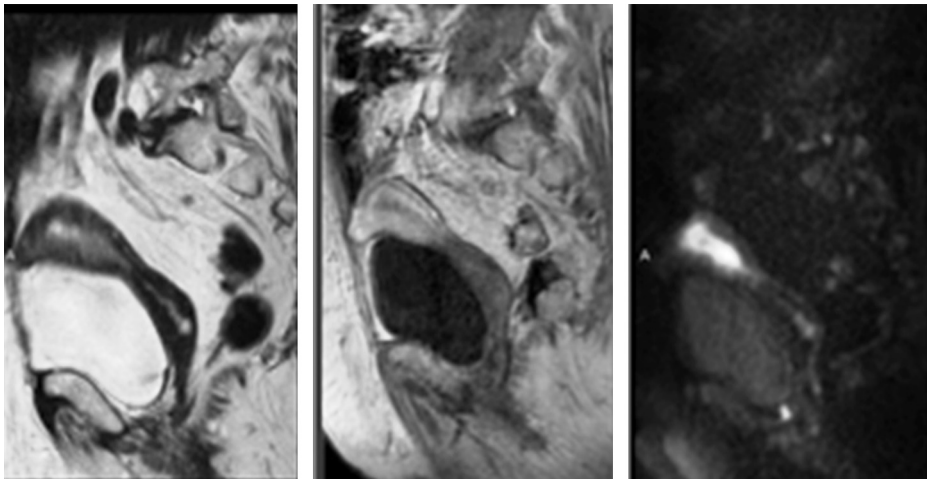

Figure 1. Comparison of T2-weighted perfusion and diffusion MRI to assess myometrial invasion of an endometrial cancer. The contrast between the tumor growing in the endometrial cavity and the adjacent myometrium is far more pronounced on the diffusion sequences than on the T2-weighted or perfusion sequences.

Cervix

Cervical cancer appears as an isointense mass on T2-weighted sequences, interrupting the physiological hypointense signal of the cervical fibrous stroma. The tumor is generally well defined on T2-weighted sequences but can be difficult to detect if it is small. Dynamic contrast enhanced MRI can be useful in this situation as cervical tumors typically enhance intensely and early (30 s) after gadolinium injection (Fig. 2). The sensitivity of dynamic sequences to detect tumors has been reported to be 78% compared to 61% for T2-weighted sequences and 39% for late T1-weighted sequences [5]. The enhancement is inside the tumor and is increased by inflammation of the normal adjacent stroma around the tumor. Measurements of tumor volume are not therefore recommended on dynamic contrast enhanced sequences. In addition, dynamic contrast enhanced sequences are reported to enable an assessment to be made of tumor microcirculation, a key factor in predicting response to radiotherapy: tumors with massive enhancement are those with high perfusion and are therefore those which are best controlled locally by radiotherapy.

Dynamic contrast enhanced MRI is useful in monitoring patients on treatment to distinguish post-radiation inflammation from residual tumor. This is an essential factor in deciding on curative surgery [9].

Pre- and post-embolization assessment for uterine fibroids

Several groups use dynamic contrast enhanced MRI in the initial pre-embolization assessment. Fibroids which show intense early enhancement respond best to embolization therapy. In addition, the change in perfusion parameters during follow-up is reported to predict the effectiveness of treatment, with an early fall in perfusion parameters in treated fibroids [10].

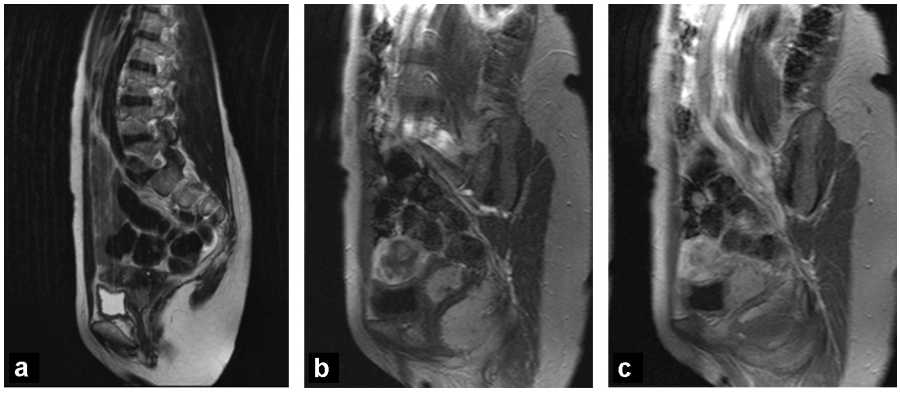

Figure 2. Comparison of conventional enhanced T2-weighted MRI and perfusion MRI to detect cervical cancer. It is difficult to distinguish the tumor on the conventionally enhanced T2-weighted sequences, whereas intense early cervical tumor enhancement enables it to be seen very easily on the early dynamic sequences taken 30 s after injection.

Appendix

Normal ovaries and functional disease

The normal ovary displays intense early enhancement with a secondary washout. The enhancement profile varies according to hormone status and phase of the menstrual cycle. The time to peak has been reported to be reduced together with an increase in signal intensity at 30 s and an increase in secondary washout in patients with polycystic ovarian syndrome.

Organic adnexal tumors

Rationale for the use of dynamic contrast enhanced MRI to characterize adnexal tumors

Preoperative characterization of adnexal tumors is essential in order to plan surgery. The distinction between benign, borderline and malignant tumors is important in order to decide on the surgical approach (laparoscopy versus laparotomy) and the type of surgery (such as cystectomy, unilateral salpingo-oophorectomy or hysterectomy with bilateral salpingo-oophorectomy). These are particularly important factors in young women when the challenge is to preserve fertility whilst offering optimal treatment. It is also an important factor in post-menopausal patients in whom surgery causes many co-morbidities and for whom monitoring via imaging may be offered. With epithelial tumors, it is also useful for the surgeon to know whether he/she is dealing with a serous or mucinous tumor (as a complementary appendectomy is performed in the latter type).

The main technique used to characterize ovarian masses is currently endovaginal ultrasound. According to the studies, the diagnostic accuracy of this investigation varies greatly. Endovaginal ultrasound is a very good method to characterize non-complex small masses. The risk of malignancy is extremely low (0.3%) for an anechogenic unilocular cyst under 50 mm in size on ultrasound. There is therefore no point in performing other imaging investigations in this situation. However, for larger masses (over 50 mm in size) or with ''complex'' masses (non-unilocular or non-anechogenic), this technique, even when combined with Doppler ultrasound, has been shown to have far poorer diagnostic accuracy (63%).

Some authors recommend a second-line diagnostic laparoscopy. This approach is debatable as laparoscopy has a poor positive predictive value (34.7%) because of the large number of false positives due to the inability to distinguish laparoscopically between a benign and malignant growth.

Several studies have shown sectional imaging techniques (MRI or CT) to have added value in characterizing ''complex or equivocal'' masses on endovaginal ultrasound [11]. MRI has been shown to be considerably superior to CT in characterizing tumors in this situation because of its excellent tissue contrast [11]. Pelvic MRI also helps in diagnosing pseudotumors, including subacute or chronic Fallopian tube diseases such as pelvic infection or adnexal torsion.

Gadolinium-enhanced investigations can identify the presence of a tissue component within the tumor, which is classically deemed to be a predictive factor for malignancy. This tissue component includes vegetations, thickens irregular septa and a solid portion [12], although this can also be seen in many benign tumors. It is therefore essential to optimize the characterization of this tissue component. Some MRI appearances have a diagnostic accuracy of over 90% in favor of benign disease. These include shading (an appearance indicating a T2 hypointensity of a specific cystic lesion in an ovarian endometrioma) or fat within the tumor (which is almost solely specific to mature cystic teratoma). In these two situations, conventional MRI is sufficient to characterize the tissue although in populations other than those with these two types of tumor, the other classical signs of malignancy (bilateral disease, predominantly solid mass, thick irregular septa, vegetations, a solid portion, lymphadenopathy and ascites) all have a diagnostic accuracy of under 75%. Additional sequences such as dynamic contrast enhanced MRI or diffusion MRI are needed for this type of tumor to improve preoperative characterization of the lesions.

Characterization of adnexal tumors

The tumor tissue forming the solid component of adnexal tumors has different microvascular features depending on whether it is benign or malignant and invasive. The microvasculature of malignant tumors over-expresses one of the VEGF receptors (VEGFR-2) and has defective pericyte coverage. This immaturity of the microvasculature wall is seen on dynamic contrast enhanced MRI as a greater maximum enhancement gradient than in benign tumors [13]. Dynamic contrast enhanced MRI can therefore play a major role in characterizing tumor tissue [14]. Three types of early enhancement curve (less than 2 min) are seen, using the adjacent myometrium as the internal reference, and correlate with histological type: curve type 1, the ''benign'' curve describes a gradual enhancement curve, curve type 2 describes an earlier enhancement curve but one which is also later than the myometrial curve with a plateau effect and the type 3 curve which is specific to invasive malignant tumors, describes a curve which is shifted to earlier than that of the myometrium [15].

Dynamic contrast enhanced MRI can also be useful to characterize solid pelvic tumors. The most common of these are the subserosal leiomyoma and the ovarian fibroma which can be difficult to distinguish on morphological criteria. These two tumors usually present as a T2-weighted hypointense mass with regular outlines. They may be homogeneous or heterogeneous and their size is non-specific. Dynamic contrast enhanced MRI can easily distinguish between these two types of tumors by showing a parallel dynamic curve to that of the adjacent myometrium in the subserosal myomas unlike the ovarian fibromas which have low late enhancement [16].

Finally, adding functional perfusion and diffusion sequences to a conventional protocol can significantly improve the diagnostic accuracy of pelvic MRI to characterize complex adnexal masses. Perfusion and diffusion sequences improve the radiologist's diagnostic accuracy by 15 and 25% respectively with a particularly significant benefit in reclassifying tumors which would otherwise have been diagnosed as malignant according to conventional MRI criteria as benign [1]. This has been shown regardless of the experience of the person interpreting the MRI. Combining all of these factors in a multivariate model can increase

diagnostic accuracy by 96%, making pelvic MRI a reliable and useful and appropriate tool in the management of adnexal masses. This is an essential clinical practice point in patients of childbearing age as it enables us to safely offer them conservative surgery and preserve their fertility. It can also help to reduce the number of unnecessary surgical procedures which are a source of morbidity, in post-menopausal patients.

One more recent study has examined the value of quantitative parameters obtained from compartmental modeling in characterizing adnexal tumors [17]. This study was performed on 54 patients and demonstrated the utility of microcirculatory parameters such as tissue perfusion (FT), the blood volume fraction (Vb), interstitial volume and area under the curve (rAUC) to distinguish benign from malignant tumors. In addition, with malignant tumors, microcirculatory parameters can distinguish malignant tumors associated with peritoneal carcinomatosis (found upon surgical exploration) from those not associated with carcinomatosis. This is useful information as no morphological imaging technique offers particularly good diagnostic accuracy to detect seeds of peritoneal carcinomatosis. Yet, this is an essential preoperative finding to enable the oncologist to decide on the best treatment option, particularly for advanced stages IIIC and IV tumors (neoadjuvant chemotherapy versus first-line surgery).

Conclusion

In conclusion, perfusion imaging has become a standard tool in many female pelvic diseases and is now an essential sequence, unavoidable in many cases.

TAKE-HOME MESSAGES

The main uses of perfusion sequences in the primary MRI indications in female pelvic disease are:

- in cervical cancer: detection of initial small tumors and distinction between post-radiation fibrosis and recurrence of tumor;
- in endometrial cancer: identification of cervical invasion;
- for pelvic masses: distinction between ovarian fibroma and fibroid and characterization of complex adnexal tumors (benign, borderline, invasive).

Clinical case report

This 28-year-old woman was referred for a pelvic MRI to characterize a pelvic mass discovered incidentally during an ultrasound performed for abdominal pain (Fig. 3).

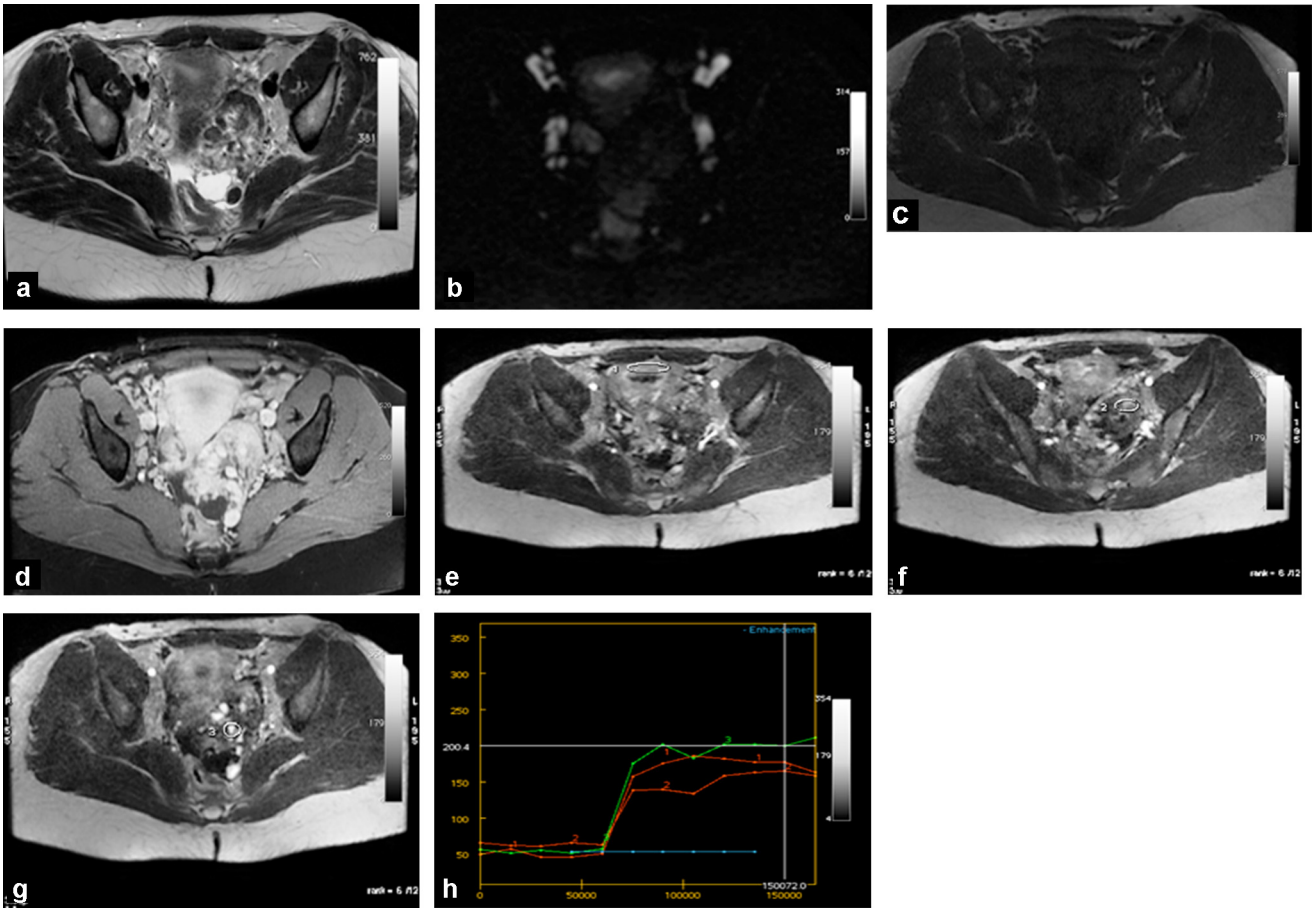

Figure 3. Images from MR and CT showing a T2-weighted axial sequence (a), a diffusion sequence (b), CT without injection (c) and a T1-weighted sequence after gadolinium (d). Dynamic section after injection (e, f, g). Perfusion curve comparing enhancement of the mass to that of the adjacent healthy external myometrium (h).

Figure 4. CT shows largish coarse central calcifications.

Questions

1. Describe the abnormalities seen on morphologicalMRI.
2. Describe the abnormalities seen on perfusion MRI.
3. Describe the abnormalities seen on diffusion MRI.
4. What is the most likely diagnosis and how are the differential diagnose excluded?

(a) Fibrothecoma
(b) Brenner's tumor
(c) Ovarian metastases
(d) Broad ligament fibroid
(e) Cystadenocarcinoma

Answers

1. This is a solid hypervascularized lateral uterine mass which is heterogeneous on a T2-weighted sequence. It is not possible to establish whether it originates from the uterus or adnexae, as the normal ipsilateral ovary cannot be seen despite the patient's young age.

2. The perfusion curves for the mass show that it enhances in parallel with the adjacent healthy myometrium, following a type 2 curve (which makes a fibrothecoma unlikely, as this classically enhances slowly and gradually, following a type 1 curve).

3. In addition, this solid mass has no hyperintensity on a diffusion sequence, which is strong diagnostic evidence in favor of benign disease and excludes the diagnoses of cystadenocarcinoma and an ovarian metastasis.

4. Therefore, only the diagnostic possibilities of a Brenner's tumor and broad ligament fibroid remain. The features of the perfusion curve which follows in parallel to the external myometrial curve variations, point towards a fibroid, which was confirmed surgically.

The patient had had a CT (Fig. 4) which can be useful at diagnosis by showing largish coarse central calcifications.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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